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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/765,067	PAGE ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 10/31/2007, has been entered.

Applicant's amendment, filed 10/31/2007, has been entered.

Claims 1 and 9 have been amended.

Claims 11-14 have been added.

Claims 1-14 are pending.

Claims 1-3 and 7-14 as they read on the elected invention of arthritis are under consideration in the instant application.

As indicated previously, given the election of the two-part dosing regime, the species election has been extended to both species of dosing indicated in the Restriction Requirement, mailed 10/4/2006, in the interest of compact prosecution.

Claims 4-6 have been withdrawn from consideration as being drawn to the non-elected invention / species.

Applicant's election of the Species where the human is afflicted with a T cell disorder / an autoimmune disease, and wherein the human is afflicted with arthritis in the Reply To Election Of Species Requirement, filed 11/06/2006, has been acknowledged.

Again, it is acknowledged that during a telephone conversation with MaryAnne Armstrong on 11/27/2006, an election was made to prosecute the species of the two-part dosing regime, as the second species election set forth in the Restriction Requirement, mailed 10/04/2006.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's amendment, filed 10/31/2007.

The rejections of record can be found in the previous Office Actions, mailed 11/29/2006 and 08/28/2007.

3. Again, applicant's previous comments that the guidelines for the arrangement of the specification are merely guidelines and are not required have been acknowledged.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. *This is a written description / new matter rejection.*

Claims 1-3 and 7-14 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:
(A) "suspension culture CHO cell expression system ... " and

(B) "in spinning culture and ... ".

Applicant's amendment, filed 10/31/2007, asserts that no new matter has been added and relies upon the disclosure on page 10 and in Example 4, page 19 of the specification for support of the amended claims.

(A) "suspension culture CHO cell expression system ... "

However, the recitation of "suspension culturing" is not readily apparent on page 10 and in Example 4, page 19 of the instant specification.

For example, it is noted that pages 21-22 of the specification is directed towards analysis of the rate of antibody synthesis and secretion from CHO cells either in growth phase or confluent stationary phase. During the course of culturing the CAMPATH-1H producing CHO cells, it became clear that even when they read confluence, antibody levels continued to accumulate in the culture medium. Here, too, the specification discloses that antibody synthesis and secretion are not diminished even when the recombinant CHO cells remain stationary for long periods.

Also, the recitation of suspension culturing per se as well as the concept of "suspension culturing" are not readily apparent on page 10 and in Example 4, page 19 of the instant specification, as currently claimed.

Therefore, reliance upon culturing CHO cells for the production of antibodies does not provide sufficient written description for "suspension culturing", as currently claimed and as asserted in applicant's REMARKS.

Also, it appears that this "limitation" has been added to conveying a critical limitation, not clearly defined in the specification as-filed and was added in an attempt to avoid or alter prior art rejections.

A showing of possession of culturing CHO cells, but not clearly describing "suspension culturing" does not satisfy the statutory mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention.

(B) "in spinning culture and ... ".

However, the recitation or the concept of generic "spinning culturing" is not readily apparent page 10 and in Example 4, page 19 in the instant specification, nor as a critical element of the claimed or disclosed invention as-filed.

Therefore, reliance upon culturing CHO cells for the production of antibodies in Techner Spinners in Example 4 of the instant specification alone does not provide sufficient written description for "spinning culturing", as currently claimed.

Also, it appears that this "limitation" has been added to convey a critical limitation, not clearly defined in the specification as-filed and was added in an attempt to avoid or alter prior art rejections.

A showing of possession of culturing CHO cells, but not clearly describing "suspension culturing" does not satisfy the statutory mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention.

Applicant's apparent reliance on generic disclosure of culturing transformed CHO cells for producing therapeutic recombinant antibodies and a specific Example employing Techner Spinners does not provide sufficient direction and guidance to the written description of "spinning cultures" in the context of claimed methods as currently claimed.

With respect to applicant's newly amended limitations indicated as (A) and (B), it is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads.

See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the priority applications as well as the specification as-filed, and would have changed the scope of the priority applications and do change the scope of the instant disclosure as-filed.

The specification as filed does not provide a sufficient written description or set forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitation", as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above.

See MPEP 714.02 and 2163.06

6. Given applicant's newly amended claims which recite "suspension culturing", "spinning culturing" and "serum-free media",

New Grounds of Rejection have been set forth herein.

Applicant's arguments, filed 10/31/2007, have been fully considered but have not been found convincing in view of the New Grounds of Rejection herein addressing applicant newly amended claims.

7. Claims 1-3 and 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adair et al. (EP 0388 151 A1) in view of Mather et al. (U.S. Patent No. 5,122,469), Zettlemeissl et al. (Biotechnology 5: 720-725, 1987), Handa-Corrigan et al. (Enzyme Microb. Technol. 11: 230-235, 1989), Schneider (J. Immunol. Methods 116: 65-77, 1989) (Schneider et al. 1989), Schneider et al. (J. Immunol. Methods. 129: 251-268, 1990) (Schneider et al. 1990), Murakami et al. (U.S. Patent No. 5,019,499) and Wolfe et al. (U.S. Patent No. 5,232,848).

The following of record incorporates the newly added references to address applicant's newly amended claims.

Adair et al. teach methods of providing for modified antibodies for diagnostic and therapeutic procedures, including specificities for tumor antigens (e.g. page 4, paragraph 5) that have been produced with glycosylation sites in a variety of host cells including CHO cells (See entire document, including Summary of the Invention and the Description of Specific Embodiments of the Invention). Adair et al. Teach the advantages of modifying the glycosylation of such antibodies includes modifying half-life, preserving properties such as activating complement, binding Fc receptors and inducing ADCC (see Background of the Invention on page 2; Summary of the Invention on pages 3-4 and Abstract). Construction of such chimeric or humanized antibodies involve recombinant expression vectors comprising the immunoglobulin heavy or light chain, introducing such vectors into CHO cells , culturing said cells, recovering said glycosylated antibodies and administering said antibodies (e.g. see Description of Specific Embodiments of the Invention).

Adair et al. differs from the claimed methods by not disclosing that the elected invention arthritis as the target of immunotherapy with CHO glycosylated antibodies.

Queen et al. teach methods of producing recombinant antibodies that can be readily produced and that are substantially less immunogenic for treating human disorders (see entire document, including Summary of the Invention and Detailed Description of the Invention), including the treatment of autoimmune diseases such as rheumatoid arthritis (e.g. see column 19, lines 19-26; column 21, paragraph 1; column 23, paragraph 2; column 26, paragraph 1; column 36, paragraphs 3-5). In addition, Queen et al. teach administering about 1 to about 200 mg of antibody per dose, with dosages of from 5 to 25 mg, including single and multiple administration depending on variables such as the severity of the disease and the patient, which would be determined the ordinary artisan, namely the treating physician at the time the invention was made (e.g. see columns 23-24).

Waldmann et al. teach recombinant antibodies, particularly antibodies to CAMPATH-1, to treat autoimmune diseases, including rheumatoid arthritis (see entire document, including Detailed description of the Invention, including Examples).

Adair et al. teach methods of providing for modified antibodies for diagnostic and therapeutic procedures, including specificities for tumor antigens (e.g. page 4, paragraph 5) that have been produced with glycosylation sites in a variety of host cells including CHO cells (See entire document, including Summary of the Invention and the Description of Specific Embodiments of the Invention). Adair et al. teach the advantages of modifying the glycosylation of such antibodies includes modifying half-life, preserving properties such as activating complement, binding Fc receptors and inducing ADCC (see Background of the Invention on page 2; Summary of the Invention on pages 3-4 and Abstract). Construction of such chimeric or humanized antibodies involve recombinant expression vectors comprising the immunoglobulin heavy or light chain, introducing such vectors into CHO cells, culturing said cells, recovering said glycosylated antibodies and administering said antibodies (e.g. see Description of Specific Embodiments of the Invention).

Adair et al. differs from the claimed invention by not teaching the known steps of culturing transfected CHO cells in serum-free medium as well as the known means of suspension / spinning culturing of cells to produce recombinant proteins of interest at the time the invention was made.

Also, it is noted that "spinning cultures" are "suspension cultures" as we

Mather et al. teach small scale and large scale production of applying methods of culturing CHO to high densities in order to improve production of recombinant proteins, including the use of serum free media, including the presence of pluronic F68 (see Preparation of Media, particularly column 10, paragraph 1; Tables 3 – 4 and Table A or Example 1; Claim 3) (see entire document, including Background of the Invention, see column 2; Summary of the Invention, column 3; Detailed Description of the Invention and Claims).

Handa-Corrigan et al. teach the use of defined serum-free media as well as the use of the cell protective agent pluronic F-68 in the growth of mammalian cells (See entire document, including Abstract, Results and Discussion and Conclusion).

Similarly, Schneider et al. 1989 disclose the optimization of hybridoma cell growth and antibody secretion in chemically defined serum-free culture media, including the use of pluronic F68 as well as Iscove's media (see entire document, including Abstract, Materials and Methods, Results and Discussion). For example, Schneider et al. 1989 teach that pluronic acid had no toxic effects on hybridoma cells, improved cell growth and increased antibody secretion (see Effect of Pluronic F68 on page 72). Schneider et al. 1989 teach the use of a totally chemically defined medium for the cultivation of cells provides several advantages over the classical serum-containing media (e.g. see Conclusion, including page 76, column 1, paragraph 3).

In addition, Schneider et al. (1989) also teach the use and advantages of using a semi-continuous mode of cultivation in spinner flasks in producing antibodies (see entire document, including Abstract and Conclusion).

Schneider et al. (1990) further provides for optimization of antibody production in spinner flasks (see entire document, including Abstract and Conclusion)

In addition to Schneider et al. 1989 and Schneider et al. 1990,
Murakami et al. (U.S. Patent No. 5,019,499) and Wolfe et al. (U.S. Patent No. 5,232,848) have been applied in this rejection to address applicant's newly amended claims reciting "spinning culture".

Murokami et al. teach the known use of various means of cultivating or culturing cells in vitro using suitable method depending on the case and for the purpose of efficiently producing the desired polypeptide (e.g., see column 3, paragraph 4), including myeloma cells (e.g., see Summary of the Invention on columns 1-2; Detailed Description of the Invention on columns 2-4 and Examples on columns 4-7) as well as serum free media, as well as spinner flasks (e.g., see column 3, paragraph 5).

While Wolfe et al. was focused on a basal nutrient medium suitable for high and low cell density culture,
Wolfe et al. teach the well known use of CHO cells in cell and the production of antibodies in a variety of production modes, such as hollow fiber bioreactors, fermenters, spinner flasks and roller bottles (e.g., see Detailed Description of the Invention, particularly column 4, paragraph 4; column 7, paragraph 3). Here, too, Wolfe et al. teach the well known use of serum-free media as well (e.g., see Background of the Invention, Summary of the Invention and Detailed Description of the Invention).

Zellemeissl et al. teach the expression of biologically active recombinant protein in CHO cells, including the ability to achieve more than 30 splittings (see entire document, including page 721, column 1, paragraph 3).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Maher et al., Handa-Corrigan et al. and Schneider to those of Adair et al. to grow CHO cells expressing recombinant antibodies, given the advantages of chemically defined serum-free media and pluronic F68 in the growth of mammalian cells, including CHO cells and/or antibody producing cells, particularly for large-scale cultivation of such cells, as taught by the secondary references. The prior art chemically defined media taught by the secondary references teach the components encompassed by the instant claims. Also, Zellemeissl et al. teach that CHO cells expressing and producing biologically active recombinant proteins could readily undergo a number of passages. Given these teachings of small scale and large scale production recombinant proteins in CHO cells over multiple passages, the

ordinary artisan would have had both motivation and a reasonable expectation of success that CHO cells could be cultured for multiple passages, which could occur from two months to greater than five months.

Given that the prior art goal was to treat certain disease, including arthritis, with therapeutic antibodies, providing the antibodies with repeated administration, particularly in a chronic disease such as arthritis, was routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such therapeutic regimens for the treatment of arthritis with therapeutic antibodies.

In contrast to applicant's assertions of record that Parehk et al. suggests that multiple administration of a glycosylated IgG for the treatment of a disease such as the elected species arthritis might be expected to increase the immunogenicity to the IgG, the combined prior art teaching provided sufficient motivation and expectation of succcess in achieving the claimed dosages, which were well within the purview of effective amounts and the multiple administration of therapeutic antibodies, which would have comprised a two-part dosing regimen, particularly given the chronic nature of many diseases/disorders, including autoimmune diseases such as arthritis.

Also, as pointed out previously, particular parameters such as dosages and modes of administration were well known and recognized as being result-effective variables (i.e., a variable which achieves a recognized result) in therapeutic regimens at the time the invention was made. In turn, the determination of the optimum or workable ranges of said variables might be characterized as routine experimentation.
For example, MPEP 2144.05, including In re Antonie, 195 USPQ 6 (CCPA 1977).

According to Adair et al., a person of ordinary skill in the art would have been motivated to produce CHO glycosylated therapeutic antibodies, given the advantages of ease and control of production of recombinant antibodies and the advantages of such modifications for altering antibody half-life and effector function(s) in human therapy.

Given providing effective amounts of therapeutic antibodies depended upon various parameters such as the nature of the disease and the patient and the desired endpoints associated with a particular disease/patient, the two-part dosing regime recited in claims 9-10 would have been obvious to the ordinary artisan in providing said effective amounts to a patient in need at the time the invention was made. The claimed dosages were well within the purview of effective amounts and the multiple administration of therapeutic antibodies, which would have comprised a two-part dosing regimen, particularly given the chronic nature of many diseases/disorders, including autoimmune diseases such as arthritis. Further, particular parameters such as dosages and modes of administration were well known and recognized as being result-effective variables (i.e., a variable which achieves a recognized result) in therapeutic regimens at the time

the invention was made. In turn, the determination of the optimum or workable ranges of said variables might be characterized as routine experimentation.
For example, see MPEP 2144.05 and In re Antonie, 195 USPQ 6 (CCPA 1977).

As to the use of multiple doses of therapeutic antibodies in the treatment of diseases, including in the treatment of arthritis, as opposed to a single doses alone,
it is noted that we find that a the methods of administration of therapeutic antibodies at the time the invention was made was a result effective variable. It has been well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As single and multiple administration of therapeutic antibodies were are known and practiced by the ordinary artisan at the time the invention was made, it would have been obvious to optimize both the mode of administration as well as dosage amounts taking into account the standard parameters of the nature of the disease and the patient and the desired endpoints associated with a particular disease/patient

Therefore, the two-part dosing regimes recited in the instant claims were obvious to the ordinary artisan at the time the invention was made.

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1742 (2007).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR, 127 S. Ct. at 1739.

This is the case here as indicated previously and in addressing applicant's previous arguments concerning "suspension culture" or applicant's new arguments concerning "spinning culture",
the claims are obvious over the prior art, which clearly taught the use of CHO cells in producing therapeutic antibodies of interest (e.g., see Adair et al.) as well as the use and advantages of serum free media, and pluronic acid in the growth of CHO cells expressing recombinant proteins, including antibodies and/or antibody-producing cells, particularly in large-scale production was known and practiced at the time the invention was made by the ordinary artisan via various known means of cultivating or culturing

cells in vitro using a suitable method depending on the case and for the purpose of efficiently producing the desired polypeptide (see secondary references).

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). See MPEP 2145.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S., 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat certain disease, including arthritis, with therapeutic antibodies, providing the antibodies with repeated administration, particularly in a chronic disease such as arthritis, was routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such therapeutic regimens for the treatment of arthritis with therapeutic antibodies.

In contrast to applicant's assertions that Parehk et al. suggests that multiple administration of a glycosylated IgG for the treatment of a disease such as the elected species arthritis might be expected to increase the immunogenicity to the IgG,

the combined prior art teaching provided sufficient motivation and expectation of succcess in achieving the claimed dosages, which were well within the purview of effective amounts and the multiple administration of therapeutic antibodies, which would have comprised a two-part dosing regimen, particularly given the chronic nature of many diseases/disorders, including autoimmune diseases such as arthritis.

Also, as pointed out previously, particular parameters such as dosages and modes of administration were well known and recognized as being result-effective variables (i.e., a variable which achieves a recognized result) in therapeutic regimens at the time the invention was made. In turn, the determination of the optimum or workable ranges of said variables might be characterized as routine experimentation.

For example, MPEP 2144.05, including In re Antonie, 195 USPQ 6 (CCPA 1977).

With respect to applicant's assertions concerning the teachings of Adair et al. and Queen et al. individually,

once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather merely asserts that the prior art does not provide sufficient suggestion or motivation to employ the claimed antibodies in the treatment of arthritis or any other glycosylation disease and does not address the teachings of the references individually and not their teachings individually or in combination.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Further, the arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Queen et al. and Waldmann et al. to those of Adair et al. to obtain CHO glycosylated antibodies to treat autoimmune diseases such as arthritis.

According to Adair et al., a person of ordinary skill in the art would have been motivated to produce CHO glycosylated therapeutic antibodies, given the advantages of ease and control of production of recombinant antibodies and the advantages of such modifications for altering antibody half-life and effector function(s) in human therapy.

Given providing effective amounts of therapeutic antibodies depended upon various parameters such as the nature of the disease and the patient and the desired endpoints associated with a particular disease/patient, the two-part dosing regime recited in claims 9-10 would have been obvious to the ordinary artisan in providing said effective amounts to a patient in need at the time the invention was made. The claimed dosages were well within the purview of effective amounts and the multiple administration of therapeutic antibodies, which would have comprised a two-part dosing regimen, particularly given the chronic nature of many diseases/disorders, including autoimmune diseases such as arthritis. Further, particular parameters such as dosages and modes of administration were well known and recognized as being result-effective variables (i.e., a variable which achieves a recognized result) in therapeutic regimens at the time the invention was made. In turn, the determination of the optimum or workable ranges of said variables might be characterized as routine experimentation. For example, MPEP 2144.05, including In re Antonie, 195 USPQ 6 (CCPA 1977).

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

As to the use of multiple doses of therapeutic antibodies in the treatment of diseases, including in the treatment of arthritis, as opposed to a single doses alone, it is noted that we find that a the methods of administration of therapeutic antibodies at the time the invention was made was a result effective variable. It has been well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As single and multiple administration of therapeutic antibodies were are known and practiced by the ordinary artisan at the time the invention was made, it would have been obvious to optimize both the mode of administration as well as dosage amounts taking into account the standard parameters of the nature of the disease and the patient and the desired endpoints associated with a particular disease/patient.

Therefore, the two-part dosing regime recited in claims were obvious to the ordinary artisan at the time the invention was made.

Applicant's arguments have not been found persuasive, given the newly added references and arguments herein as the current rejection applies to applicant's newly amended claims.

8. Claims 1, 2 and 7-10 are provisonally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 12, 17, 18, 21-28, 30, 31, 37, 39-48 of copending USSN 10/145,992 in view of Mather et al. (U.S. Patent No. 5,122,469) (1449), Zettlemeissl et al. (Biotechnology 5: 720-725, 1987) (1449); Handa-Corrigan et al. (Enzyme Microb. Technol. 11: 230-235, 1989) and Schneider (J. Immunol. Methods 116: 65-77, 1989) (Schneider et al. 1989), Schneider et al. (J. Immunol. Methods. 129: 251-268, 1990) (Schneider et al. 1990), Murakami et al. (U.S. Patent No. 5,019,499) and Wolfe et al. (U.S. Patent No. 5,232,848) essentially for the reasons of record and that addressed above in Section 7.

Given the election of species of treating autoimmunity / arthritis in the instant application and of the election of species of treating non-Hodgkin's lymphoma in the copending application USSN 10/145,992,

The claims drawn to species diseases / conditions (e.g. arthritis, lymphoma) of the instant and copending applications are not included in this provisional double patenting rejection.

The instant claims as well as the patented claims either anticipate or render obvious one another, given that both are drawn to the same or nearly the same methods of treating patients suffering from diseases or disorders with therapeutic antibodies that have been glycosylated in a CHO expression system. Although the instant claims do not recite the particular serum free medium and pluronic acid of the instant claims, These modifications were obvious in view of the teachings of Mather et al. (U.S. Patent No. 5,122,469) (1449), Zettlemeissl et al. (Biotechnology 5: 720-725, 1987) (1449); Handa-Corrigan et al. (Enzyme Microb. Technol. 11: 230-235, 1989) and Schneider (J. Immunol. Methods 116: 65-77, 1989) for the reasons set forth in copending USSN 10/145,992. For example, the claimed inventions encompass the known steps of culturing transfected CHO cells in serum-free medium, including the known use of pluronic F68 as a cell protectant.

Mather et al. teach small scale and large scale production of applying methods of culturing CHO to high densities in order to improve production of recombinant proteins, including the use of serum free media and the ingredients recited in the instant claims, including the presence of pluronic F68 (see Preparation of Media, particularly column 10, paragraph 1; Tables 3 – 4 and Table A or Example 1; Claim 3) (see entire document, including Background of the Invention, see column 2; Summary of the Invention, column 3; Detailed Description of the Invention and Claims).

Handa-Corrigan et al. teach the use of defined serum-free media as well as the use of the cell protective agent pluronic F-68 in the growth of mammalian cells (See entire document, including Abstract, Results and Discussion and Conclusion).

Similarly Schneider discloses the optimization of hybridoma cell growth and antibody secretion in chemically defined serum-free culture media, including the use of pluronic F68 as well as Iscove's media (see entire document, including Abstract, Materials and Methods, Results and Discussion). Schneider teach that pluronic acid had no toxic effects on hybridoma cells, improved cell growth and increased antibody secretion (see Effect of Pluronic F68 on page 72). Schneider teach the use of a totally chemically defined medium for the cultivation of cells provides several advantages over the classical serum-containing media (e.g. see Conclusion, including page 76, column 1, paragraph 3).

Zellemeissl et al. teach the expression of biologically active recombinant protein in CHO cells, including the ability to achieve more than 30 splittings (see entire document, including page 721, column 1, paragraph 3).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Maher et al., Handa-Corrigan et al. and Schneider to grow CHO cells expressing recombinant antibodies, given the advantages of chemically defined serum-free media and pluronic F68 in the growth of mammalian cells, including CHO cells and/or antibody producing cells, particularly for large-scale cultivation of such cells, as taught by the secondary references. The prior art chemically defined media taught by the secondary references teach the components recited in claims 24-27 (see citations above). Also, Zellemeissl et al. teach that CHO cells expressing and producing biologically active recombinant proteins could readily undergo a number of passages. Given these teachings of small scale and large scale production recombinant proteins in CHO cells over multiple passages, the ordinary artisan would have had both motivation and a reasonable expectation of success that CHO cells could be cultured for multiple passages, which could occur from two months to greater than five months.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. It would have obvious to one of ordinary skill in the art that the recitation of a CHO expression system in the copending claims would have included the advantages of a serum-free media and pluronic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's remarks, filed 10/31/2007, indicating that "should it be determined that a terminal disclaimer is necessary after allowable subject matter has been agreed, applicant will file such disclaimer", is acknowledged.

The provisional rejection is maintained for the reasons of record.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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